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EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1616	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/750,390	PERRICONE ET AL.	
	Examiner	Art Unit	
	Ernst V. Arnold	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-14 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 3/29/04, 10/15/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-14 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method wherein the surfactant is a siloxylated polyether and a polydimethylsiloxane lubricant, does not reasonably provide enablement for a method with any and all surfactants and lubricants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims without an undue amount of experimentation.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: 1) scope or breadth of the claims; 2) nature of the invention; 3) relative level of skill possessed by one of ordinary skill in the art; 4) state of, or the amount of knowledge in, the prior art; 5) level or degree of predictability, or a lack thereof, in the art; 6) amount of guidance or direction provided by the inventor; 7) presence or absence of working examples; and 8) quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure. When the above factors are

weighed, it is the Examiner's position that one skilled in the art could not practice the invention without undue experimentation.

1) Scope or breadth of the claims

The claims are broader in scope than the enabling disclosure. The specification merely discloses, without more, a method wherein the surfactant is a siloxylated polyether and a polydimethylsiloxane lubricant (page 7, [0018]). However, Applicant is purporting to use all surfactants and lubricants.

2) Nature of the invention

The nature of the invention is directed to methods of making insulin compositions.

3) Relative level of skill possessed by one of ordinary skill in the art

The relative level of skill possessed by one of ordinary skill in the art of drug delivery research is relatively high, as a majority of lead investigators directing scientific research and development in this particular technological area possess an Ph.D. in a scientific discipline such as organic synthetic chemistry, polymer chemistry, medicinal chemistry, biochemistry, pharmacology, biology or the like.

4) State of, or the amount of knowledge in, the prior art

Modi (US 6,193,997) discloses method of making pharmaceutical composition comprising mixing an alkali metal lauryl sulfphate (surfactant) with an oil, such as borage or primrose oil (lubricant), and a phospholipid such as lecithin or saturated lecithin where the pharmaceutical agent can be insulin (Claims 7-11).

5) Level or degree of predictability, or a lack thereof, in the art

The art teaches that polyoxethyleneamine, a surfactant found in the herbicide Roundup, is in fact poisonous (Cox, Journal of Pesticide Reform 1998, 8(1), page 30). The art teaches that vesicle formulations are dependent on the ratio and type of ingredients and merely mixing soybean oil, which has a phosphatidylcholine component, with a lipid component can result in very thick solid consistency compositions thus establishing that not just any mixture of components will result in the desired product (Mathur US 5,439,967 see column 5, Table 2, line 31 through column 6, line 32).

6) Amount of guidance or direction provided by the inventor

Applicant was required to provide in the specification additional guidance and direction with respect to how use the claimed subject matter in order for the application to be enabled with respect to the full scope of the claimed invention. Although the instant specification discloses that a method wherein the surfactant is a siloxylated polyether and a polydimethylsiloxane lubricant can be used, it remains silent on the using any and all lubricants and surfactants.

7) Presence or absence of working examples

The specification fails to provide scientific data and working embodiments with respect to any and all the various surfactants and lubricants that can be used in the invention.

8) Quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure

One of ordinary skill in the art would have to conduct a myriad number of experiments comprising picking and choosing surfactants and lubricants, some of which have been shown to be poisonous, and mix the surfactants and lubricants in an unknown ration with the insulin carrier in the hopes of producing a carrier to entrap the insulin. Essentially, one of ordinary skill

in the art has to figure out how to do this themselves. As a result, one of ordinary skill in the art would be required to conduct an undue amount of experimentation.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 contains the trademark/trade name E200 and E400. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a type of polyglycol and, accordingly, the identification/description is indefinite.

For the purpose of examination, the Examiner is interpreting polyglycol E200 and polyglycol E400 to mean a polyglycol of 200 molecular weight and a polyglycol of 400 molecular weight as suggested in the specification on page 6.

Claim Rejections - 35 USC § 112

Claim 4, which is dependent on claim 2, recites the limitation "E200" and "E400". There is insufficient antecedent basis for this limitation in the claim. Claim 2 does not recite the limitation "E200" and "E400". Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Guo et al. (Drug Delivery 2000, 7, 113-116).

Gou et al. teach methods to synthesize nano-sized vesicles comprised of soybean lecithin for the purpose of transdermal delivery of insulin (See: Abstract; Materials and Methods, pages 113-114; Results, page 114-115 and Discussion page 116). Soybean lecithin is enriched with polyenylphosphatidylcholine (instant specification page 4 [0012]). It is the Examiner's position that the method of Gou et al. would stabilize insulin at room temperature in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 102

Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Modi (US 6,193,997).

Modi discloses method of making pharmaceutical composition comprising mixing an alkali metal lauryl sulfphate (surfactant) with an oil, such as borage or primrose oil (lubricant), and a phospholipid such as lecithin or saturated lecithin where the pharmaceutical agent can be insulin (Claims 7-11). Modi discloses an example of 1000 mg insulin crystals suspended in 150 ml of 0.3 M HCl, stirred, neutralized and diluted to provide 100 units/mL of insulin (Column 8 Example 1). Modi discloses that insulin is present from 2 to 4 wt/wt % of the final formulation (column 6, lines 65-67). It is the Examiner's position that Modi distinguishes between saturated lecithin and lecithin that is unsaturated and thus reads on instant claim 3. It is the Examiner's position that the method of Modi would stabilize insulin at room temperature in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 102

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Hansen et al. (US 4,614,730).

Hansen et al. disclose a method of making an insulin composition by dissolving semi-synthetic human insulin in 100 ml of 0.02 N HCl and preparing a carrier comprising dioctanoyl, L-alpha-phosphatidylcholine dissolved in distilled water. The carrier was added to the insulin solution and diluted to 1000 ml with water and produced a product with a stability factor of 65 (Columns 7-8, example 22, for example).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kikuchi et al. (U.S. Patent No. 4,687,661) in view of Patel et al. (U.S. Patent No. 6,294,192) and Chaiyawat et al. (US 6,538,061) and Brieva et al. (US 5,985,298) and Modi (US 6,193,997).

With respect to the scope of enablement rejection above, this rejection is directed to the scope that is enabled which is namely where the surfactant is a siloxylated polyether and the lubricant is polydimethylsiloxane.

Applicant claims a method of formulating an insulin composition comprising preparing a carrier having a phosphatidylcholine component.

Determination of the scope and content of the prior art

(MPEP 2141.01)

The reference of Modi et al. is described in detail above and that discussion is hereby incorporated by reference. The reference of Modi et al. is relied upon for the teaching of insulin preparation in acid.

Kikuchi et al. teach a general method for the preparation of liposomes derived from egg yolk or soybean phosphatidylcholine with a non-volatile organic solvent, such polyethylene glycol, used alone or in combinations (See: Abstract; Column 2, lines 18-50; and claims 1 and 2, for example). Kikuchi et al. teach warming the materials to easily mix the materials and teach temperatures up to 70 C (column 2, lines 65-68 and column 3, lines 1-4). Kikuchi et al. teach warming the aqueous medium containing the drugs (column 3, lines 18-23). Kikuchi et al. teach cooling the composition to room temperature (column 5, lines 5-6). Kikuchi et al. teach preparing colorless and clear phosphatidylcholine solutions (Column 4, line 64 to column 5, line 2). The drugs that can be encapsulated into the liposomes include proteins such as insulin (Column 3, lines 55-59). Kikuchi et al. teach phosphatidylcholine compositions where, for example, the phosphatidylcholine component is comprised of 9.4 g of glycerin and 2.2 g of egg yolk lecithin (total = 11.6 g) and 0.164 g of dicetyl phosphate for a 98.6% by weight phosphatidylcholine component and 1.4% by weight surfactant component (Column 4, lines 33-37). Kikuchi et al. dilute the 98.6% by weight phosphatidylcholine component solution with 300 ml of a 0.5% aqueous solution of sodium salicylate, a known preservative, to ultimately produce a sodium salicylate encapsulating liposome suspension (Column 4, lines 38-48).

Patel et al. teach a pharmaceutical composition for the topical/transdermal delivery of therapeutic agents comprised of at least one hydrophobic and at least one hydrophilic surfactant as well as solubilizers and mixtures of solubilizers. (Column 25, lines 15-19 and lines 52-53). Polyethylene glycols of average molecular weight of about 200 to about 6000, with PEG-400 a preferred solubilizing agent, are disclosed (Column 25, lines 15-63). Patel et al. disclose that the typical amount of solubilizer present in the composition will be in the range of about 1% to about

100% by weight (Column 26, lines 12-14). Patel et al. teach that hydrophobic surfactants can be in the range of about 1% to about 60% by weight of the hydrophilic surfactant (Column 21, lines 30-31). Patel et al. defines a number of hydrophobic surfactants as oils (Column 9, lines 8-13 and Column 10, lines 1-13; and Table 5, for example). The Examiner is interpreting the addition of such hydrophobic surfactants to mean the addition of a lubricant. Patel et al. further disclose the addition of other additives including preservatives (Column 26, lines 16-21). Methyl paraben is one of the most commonly known preservatives and would be immediately envisaged by one of ordinary skill in the art. Petal et al. is relied upon for teaching the addition of polyethylene glycols to the composition.

Chaiyawat et al. teach cosmetic compositions comprised of silicone fluids of low viscosity, less than 100 cSt at 25 °C, which exist as fluids at or near room temperature (Column 10, lines 48-59). The lubricious silicone fluids include polydimethylsiloxane polymers (dimethicone) (Column 10, lines 60-67 and Column 11, lines 1-4). Furthermore, Chaiyawat et al. teach that such compositions are suitable as hormone carriers (Column 12, lines 35-38 and 66) as well as drug delivery systems for topical administration of medicinal compositions to the skin (Column 12, lines 55-57). Chaiyawat et al. is relied upon for the teaching of adding polydimethylsiloxane lubricants to the composition.

Brieva et al. teach cosmetic compositions comprised of non-volatile silicones, such as Dow 190 (a surfactant), for improved long lasting adherence to the skin of cosmetics (Column 1, lines 4-42; Column 3, lines 53-65). Brieva et al. is relied upon for teaching the addition of Dow 190 surfactant to the composition.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. Kikuchi et al. do not expressly disclose a method of making a phosphatidylcholine component comprising 45% w/w phosphatidylcholine, 50% w/w polyglycol E200 and 5% polyglycol E400.

2. Kikuchi et al. do not expressly disclose a method of making a composition comprising 53.25% w/w phosphatidylcholine component, 1.00% w/w surfactant, 1.00% w/w lubricant, and 0.75% w/w methyl paraben and 44% water wherein the surfactant is a siloxylated polyether and the lubricant is a silicone fluid.

3. Kikuchi et al. do not expressly teach a method wherein the insulin is human recombinant insulin prepared in 0.01 N HCl at a concentration of 50 mg/ml or mixing the insulin solution into the carrier for at least one hour and when mixed into said carrier produces an insulin composition having a concentration of 20 mg/ml.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the phosphatidylcholine preparation of Kikuchi et al. with a combination of PEG 200 and PEG 400 as suggested by Patel et al. to produce the instantly claimed invention.

One of ordinary skill in the art would have been motivated to do this because addition of the low molecular weight PEG would enhance the solubility of poorly water soluble therapeutic

agents (Patel et al. Column 25, lines 15-18). The specific w/w ratio of the low molecular weight PEGs to the phosphatidylcholine component in the composition is deemed merely a matter of judicious selection and routine optimization of conventional working conditions, which is well within the purview of one of ordinary skill in the art as suggested by Patel et al. (Column 26, lines 1-2). Kikuchi et al. suggest warming the components and the choice of 40 C is merely a matter of judicious selection by one of ordinary skill in the art.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of making the carrier composition of Kikuchi et al. to include lubricious silicone fluids, as suggested by Chaiyawat et al., and siloxylated polyethers such DOW 190, as suggested by Brieva et al., and produce the instantly claimed invention.

One of ordinary skill in the art would have been motivated to do this because Chaiyawat et al. disclose that the addition of such emollients improves the appearance of the skin, reduces flaking and tends to remain on the surface of the skin (Column 10, lines 60-66). Therefore, by adding silicone fluids not only are the aesthetics of the carrier compound improved from a patient standpoint but also the drug delivery capabilities. One of ordinary skill in the art would have been motivated to add DOW 190 because it would have been desirable to increase the adherence of the drug carrier to the skin for optimal drug delivery (Brieva et al. Column 1, lines 41-42).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform a method wherein the insulin is human recombinant insulin prepared in 0.01 N HCl at a concentration of 50 mg/ml or mixing the insulin solution into the

carrier for at least one hour and when mixed into said carrier produces an insulin composition having a concentration of 20 mg/ml.

One of ordinary skill in the art would have been motivated to do this because Modi teaches preparing insulin in diluted hydrochloric acid. It is the Examiner's position that insulin renders obvious human recombinant insulin to one of ordinary skill in the art. It is the Examiner's position that an acid concentration of 0.01N HCl or an insulin concentration of 50 mg/mL or a final concentration of 20 mg/mL after mixing for at least one hour is merely routine optimization of the composition by one of ordinary skill in the art in the absence of evidence to the contrary.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (6:15 am-3:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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